REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claims Amendments:

Claim 1 has been amended to recite "delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor". Support for this recitation can be found, for example, in the original claim 1 and at page 5, lines 23-24.

Claims 8-13 have been amended to depend from claim 1 instead of 1(a) or 1(b) in view of amendments of claim 1. Similarly, claim 14 has been amended to no longer recite steps (a) and (b) in view of the amendments of claim 1.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Rejection Under 35 U.S.C. §102:

The rejection of claims 1, 7 and 10-13 under 35 U.S.C. §102 as allegedly being anticipated by Kooby et al. (FASEB Journal 13:1325-1334, 1999) is obviated in part and traversed in part as set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

Claim 1, as amended, is directed to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of the virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration consisting of delivering on the same day a

composition comprising the virus to multiple sites inside the solid tumor, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor. Claims 7 ans 10-13 depend from claim 1, thus recite all the elements of claim 1.

Kooby et al. teach the use of a herpes virus, G207, in the treatment of human colorectal cancer and liver metastases. Kooby et al. teach an injection of 50 μl of viral composition into a tumor of 50 mm^3. However, the claimed invention requires delivery to multiple sites into a tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor. Accordingly, Kooby et al. do not teach each and every element of the claimed invention.

The Office Action alleges that the original claim 1(a), which requires delivery to multiple sites, can be interpreted to encompass a single injection of large volume (page 4, last paragraph of the Office Action). The rationale, according to the Office Action, is as follows:

> it is noted that the specification does not explicitly define "multiple sites inside the tumor", but does indicate, "Alternatively, the virus can be delivered to a single site in a large amount of liquid, which enables a wider spread of the virus" (See p.14, lines 5-10 of the instant specification). Therefore, claims 1(a) can be interpreted to encompass delivering a single injection of a large volume of the virus... to a tumor resulting in the viral composition spreading to other sites (i.e. cells) inside the tumor.

Applicants disagree. Page 14, lines 5-10 of the specification actually teaches (emphasis added):

> In the present invention, two methods are used to increase the efficiency of virus delivery to solid tumors. The virus can be injected at multiple sites within the tumor, particularly in the outer portion of the tumor. ..... Alternatively, the virus can be delivered to a single site in a large amount of fluid, which enables a wider spread of the virus (Figure 1C).

Clearly, two methods are taught in this section: one involves multiple injections and the other is a delivery of large amount of fluid to a single site[1]. There is no indication that multiple injections can be interpreted as a single injection of large volume. Furthermore, it is established law that the words of a claim must be given their "plain meaning" unless they are defined in the specification. *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); MPEP 2111.01. If "multiple" is not explicitly defined in the specification, it should be given its plain meaning, which is "two or more" (see, *e.g.*, *The American Heritage Dictionary*, Second College Edition). Therefore, the element of delivery to multiple sites, required in the claimed invention, can not be interpreted as a single injection.

Accordingly, Kooby et al. do not teach each and every element of the claimed invention, particularly the element of delivery to multiple sites into a tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor. Therefore, the requirement under 35 U.S.C. §102 is not met, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103:

A. The rejection of claims 1-6 and 14-21 under 35 U.S.C. §103(a) as allegedly being unpatentable over Kooby et al. (FASEB Journal 13:1325-1334, 1999) in view of Lee et al. (WO 99/08692) is respectfully traversed for the following reasons.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ

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[1]It should be noted that the specification also teaches that these two methods can be combined. See, e.g., page 5, lines 23-24: "The administrations at multiple sites and large volume are not mutually exclusive. It is contemplated that these two modes of administration may be combined."

2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

As discussed above, the claimed invention relates to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of the virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration consisting of delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor.

Kooby et al. have been discussed above. The reference teaches the use of a herpes virus, G207, in the treatment of human colorectal cancer and liver metastases, such as an injection of 50 μl of viral composition into a tumor of 50 mm^3. Kooby et al. do not teach or suggest delivery to multiple sites into the tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor. Lee et al. teach the use of reovirus in reducing tumor growth, but do not specify that delivery of a virus to multiple sites in the tumor mass on the same day, or delivery of a composition in a volume that is about 10%-100% of the volume of the tumor, are advantageous. Therefore, the combination of Kooby et al. and Lee et al. still do not teach or suggest delivery to multiple sites into the tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor.

The Office Action states that Lee et al. teach the administration of single doses or multiple doses, and the multiple doses can be administered concurrently or consecutively. Applicants submit that Lee et al. do not specifically teach or suggest delivery to multiple sites into the same tumor on the same day, or delivery of a volume that is between about 10% to about 100% of the volume of the tumor per injection site. Neither do Kooby et al. or Lee et al. provide a motivation or suggestion to modify the combined teachings to arrive

at the claimed invention, which requires delivery to multiple sites into the tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor.

Therefore, this rejection does not satisfy all the required criteria under 35 U.S.C. §103, and its withdrawal is respectfully requested.

2. The rejection of claims 1, 8 and 9 under 35 U.S.C. §103(a) as allegedly being unpatentable over Kooby et al. (FASEB Journal 13:1325-1334, 1999) in view of Barber et al. (U.S. Patent No. 5,662,896) is respectfully traversed as set forth below.

The claimed invention and Kooby et al. are discussed above. The claimed invention relates to a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of the virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration consisting of delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor. Kooby et al. teach the use of a herpes virus, G207, in the treatment of human colorectal cancer and liver metastases, such as an injection of 50 μl of viral composition into a tumor of 50 mm^3.

Barber et al. relate to methods for inhibiting tumor growth using recombinant viral vectors. The vector encodes an anti-tumor agent, such as an immune activator or a proliferation inhibitor. Expression of the anti-tumor agent leads to either (1) direct inhibition of tumor cell division, or (2) immune cell mediated tumor cell lysis, or both, resulting in reduced tumor growth (see, for example, column 5, lines 27-36 of Barber et al.). Therefore, the viral vector is used as a vehicle to express the anti-tumor agent. While Barber et al. teach that the viral vector may be injected several times in several different locations within the body of the tumor (column 11, lines 6-8 of Barber et al.), the reference does not teach or suggest delivery to multiple sites in a tumor on the same day.

Furthermore, Barber et al. teach away from the claimed invention. The reference teaches the administration of about one tenth to two-tenths of a milliliter of a viral vector into tumors that are about 1-4 mm^3 in volume (column 37, lines 38-45), namely an injection volume of 25-200 fold of that of the tumor[2]. In contrast, the claimed invention requires that the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor.

Accordingly, there is no motivation or suggestion in the combination of Kooby et al. and Barber et al. to modify the combined teachings to arrive at the claimed invention. No reasonable expectation of success can be found, and the combination does not teach each and every element of the claimed invention, in particular a delivery to multiple sites in a tumor on the same day, wherein the volume of the composition delivered per site is between about 10% to about 100% of the volume of the tumor.

In view of the above, the claimed invention is not obvious in view of the combination of Kooby et al. and Barber et al., and withdrawal of the rejection is respectfully requested.

Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

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[2]One milliliter corresponds to one cm^3, which equals to 1000 mm^3. Therefore, one tenth to two-tenths of a milliliter corresponds to 100 to 200 mm^3. An injection of 100 to 200 mm^3 into a tumor of 1-4 mm^3 constitutes a delivery volume of 25 fold (injection of 100 mm^3 into a tumor of 4 mm^3) to 200 fold (injection of 200 mm^3 into a tumor of 1 mm^3).

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is invited to call the undersigned at (650) 622-2340.

Respectfully submitted,

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